Bupivacaine Levels in Plasma and Cerebrospinal Fluid Following Peridural Administration

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Plasma levels of bupivacaine following peridural administration of 150 mg bupivacaine hydrochloride with epinephrine to 12 patients, 150 mg without epinephrine to five patients, and 225 mg with epinephrine to six patients were determined. Cerebrospinal fluid levels in five of the patients in the first group were also studied. Peak plasma levels were attained in 20 min in all of the above groups. These levels were 1.14, 1.26 and 2.33 μg/ml, respectively. The peak CSF level, 30.6 μg/ml, was observed 30 min after administration. These levels are generally comparable to those that might be expected after administration of equivalent doses of the more-established local anesthetics. The post-absorption/distribution half-life of bupivacaine in both plasma and CSF ranged from 2.4 to 3.6 hours, which is not significantly different from the half-lives of shorter-acting drugs such as lidocaine, prilocaine, and mepivacaine. It is concluded that the relatively long duration of action of bupivacaine is related not to its overall retention in the body but rather to its binding to nerve tissue. (Key words: Bupivacaine; Plasma levels; Cerebrospinal fluid levels; Peridural anesthesia; Biological half-life.)

BUPIVACAINE HYDROCHLORIDE (LAC-43, Marcaine, 1-n-butyl-DL-piperidine-2-carboxylic acid-2,6-dimethylanilide hydrochloride) is a new local anesthetic agent which was synthesized by Ekenstam et al. Despite a close structural relationship to mepivacaine (Carbocaine), its potency and duration of action are similar to those of tetracaine (Pontocaine). Numerous clinical studies, particularly in Europe, attest to the potency and long duration of action of bupivacaine after a variety of anesthetic procedures. In spite of these extensive investigations, little is known of bupivacaine's distribution in, and elimination from, the body, particularly as compared with the more established local anesthetics. The present investigation was carried out to determine both CSF and plasma concentrations of bupivacaine after administration, with and without epinephrine, for peridural anesthesia.

Methods

Twenty-three patients undergoing a variety of elective surgical procedures were studied. Their ages ranged from 27 to 71 years (mean, 52.7); weights ranged from 120 to 212 pounds (mean, 160). The patients were part of a larger population of patients in whom the clinical aspects of bupivacaine administration were being investigated, with their consent. In all cases, peridural analgesia was induced with bupivacaine, administered by the modified pressure technique at the first lumbar interspace. Premedication usually consisted of pentobarbital (Nembutal), 100 mg at bedtime, except in patients more than 60 years old, who received chloral hydrate, 0.5 to 1 g, with sodium secobarbital (Seconal sodium), 50 to 100 mg, two hours preoperatively, and meperidine (Demerol), 100 mg, with scopolamine, 0.5 mg, one hour preoperatively. Thiomyal sodium (Surital) was frequently administered before administration of peridural analgesia.

Three groups of patients were investigated: twelve patients received 150 mg bupivacaine hydrochloride with epinephrine (30 ml of 0.5 per cent solution with epinephrine 1:200,000); five received 150 mg bupivacaine hydrochloride alone (30 ml of 0.5 per cent solution); six received 225 mg bupivacaine hydrochloride with epinephrine (30 ml of 0.75 per cent solution with epinephrine 1:200,000).

Heparinized blood samples were collected from each patient from an antecubital vein, 5, 10, 15, 30, and 45 min, and 1, 1.5, 2, 3, 4, and 5 hours after administration of bupivacaine. Plasma was separated and stored at 4°C until analyzed. In five patients receiving 150 mg bupivacaine hydrochloride with epinephrine,
cerebrospinal fluid (CSF) samples (2 ml) were obtained 5, 10, 20, 30, and 45 min, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 hours after drug administration, using a previously described technique.\textsuperscript{13} Samples were stored at 4°C until analyzed.

The concentrations of bupivacaine in plasma and CSF samples were determined by a modification of the gas chromatographic method developed by Asling \textit{et al.} for the analysis of mepivacaine.\textsuperscript{13} A Varian gas chromatograph, model 1740, equipped with a flame ionization detector was used, along with a 5-foot × 3/8-inch stainless steel column packed with 3 percent OV-17 coated on Gas Chrom Q, 100/120 mesh. Operating conditions were: oven temperature, 225°C; nitrogen flow rate, 30 ml/min; hydrogen flow rate, 30 ml/min; air flow rate, 300 ml/min. The extraction and concentration procedures were as described\textsuperscript{13} except that cyclizine hydrochloride, 0.4 μg/ml in distilled water, was used as the internal marker. In analyzing plasma specimens, 1-ml samples were usually taken, whereas only 0.05 to 0.1 ml of CSF was used. Sample volumes of CSF were adjusted to 1 ml with distilled water. Under the above conditions, cyclizine had a retention time of 4.1 min and was well separated from bupivacaine, retention time 9.8 min. Both peaks were sharp and symmetrical, and the calibration curve was linear over the range 0.05 to 5 μg/ml, using a 1-ml sample. Recoveries from blood, CSF and aqueous solutions were identical, and no interfering peaks were obtained from “blank” plasma and CSF samples.

Results and Discussion

Mean plasma levels (twelve patients) and mean CSF levels (five patients) obtained after peridural administration of 150 mg bupivacaine hydrochloride with epinephrine are shown in Figure 1. A maximum bupivacaine plasma level of 1.14 μg/ml was observed 20 min after drug administration. A small “distribution nose” was apparent, indicating an absorption process of a magnitude comparable to that of the distribution process(es). However, after an hour the plasma level declined exponentially, with a half-life \( t_{1/2} \) of 2.5 hours. The CSF levels had a time course similar to that of the plasma levels except that the maximum concentration, 30.6 μg/ml, was observed at 30 min and the “distribution nose” was more pronounced. However, after 1.25 hours CSF levels showed exponential decay, with a half-life similar to that of plasma, \( t_{1/2} \) = 2.6 hours.

Figure 2 illustrates mean plasma levels (five patients) of bupivacaine obtained after administration of 150 mg bupivacaine hydrochloride without epinephrine. A slightly higher peak plasma level, 1.26 μg/ml, was observed compared with the same dose administered with epinephrine. However, in all other respects the plasma concentration/time curves were virtually identical: time of peak level, 20 min; half-life, 2.4 hours. Significantly higher plasma levels were observed after the administration of 225 mg bupivacaine hydrochloride with epinephrine to six patients (fig. 3). The maximum level, 2.33 μg/ml, occurred 20 min
after administration and the post-absorption/distribution plasma half-life, 3.6 hours, was similar to that previously described.

Ekblom and Widman reportedly obtained plasma levels between 0.5 and 1 μg/ml after peridural anesthesia with 1.2–1.4 mg bupivacaine hydrochloride/kg body weight. Blood levels were followed for two hours after peridural administration of 100 mg bupivacaine hydrochloride with epinephrine (1:200,000) by Fujimori et al.; peak levels in 22 patients varied from 0.59 to 1.94 μg/ml (mean, 0.92 μg/ml) and occurred between 10 and 60 min after administration (mean, 30 min). In a similar study, after administration of 2 mg/kg bupivacaine hydrochloride with epinephrine (1:200,000), Yoshikawa et al. found that the peak blood level occurred between 10 and 30 min, with a range of 0.5 to 1.8 μg/ml (four patients). More recently, Moore et al. stated that following a single peridural dose of 150 mg bupivacaine hydrochloride with epinephrine (1:200,000) peak venous blood levels of 0.4 to 1.0 μg/ml may be expected to occur within 15 to 20 min. In twelve pregnant patients, Thomas et al. observed peak plasma levels between 0.22 and 0.60 μg/ml, 15 to 30 min following peridural administration of 50 mg bupivacaine hydrochloride with epinephrine (1:200,000). Taking into consideration hematocrit and dosage differences, it appears that the present results are similar to, and consistent with, those reported earlier with respect to time of occurrence and magnitude of the peak plasma level.

Systemic toxicity is always a potential hazard after administration of local anesthetics into the peridural space. Based upon intravenous infusion studies in dog, Jorfeldt et al. suggest that bupivacaine blood levels of 4 μg/ml or greater are necessary to evoke convulsions in man. This indicates that with the doses used in the present study it is unlikely that such toxic manifestations will be observed, and this is supported by clinical experience.

In contrast to the findings with lidocaine (Xylocaine), prilocaine (Citanest), and mepivacaine, the addition of epinephrine (1:200,000) did not have a significant effect on the plasma levels of bupivacaine; the reasons for this are unclear.

It is of interest to compare the plasma and CSF levels obtained in the present study with those reported after peridural administration of lidocaine, prilocaine, and mepivacaine. To do so it is necessary to assume that the various administration techniques are comparable and that the magnitudes of peak blood/plasma or CSF levels are proportional to the doses administered. Further research is needed to substantiate these suspicions. Additionally, the use of these compounds should be further evaluated in patients with high-risk conditions.
thermore, in converting the present bupivacaine plasma levels to blood levels it is assumed that only a small fraction of the bupivacaine in the blood is distributed outside the plasma. Initial investigations indicated that this is reasonable, because the erythrocyte: plasma ratio for bupivacaine at a total blood concentration of 1 μg/ml is about 0.1–0.2 (Wilkinson, unpublished data).26

Such calculations indicate that the peak CSF level of 30.6 μg/ml after 150 mg bupivacaine hydrochloride with epinephrine is slightly higher than might be expected from an equivalent dose of lidocaine.20 No similar data are available for either prilocaine or mepivacaine administered with epinephrine. On the other hand, blood levels after administration of bupivacaine with or without epinephrine are comparable to those observed after lidocaine administration. In turn, these levels are slightly higher and lower than after administration of equivalent doses of prilocaine and mepivacaine, respectively.

Bupivacaine is considered by all investigators to be a long-acting anesthetic. For example, in our previous clinical studies 21 we found that the duration of action after peridural injection of 100–150 mg of bupivacaine hydrochloride with epinephrine (1:200,000) was between 4.0 and 7.5 hours (average, 5.5 hours). Little is known of the relationship between local anesthetic effect and drug concentration in the biophase or even in the affected tissue. However, in the presence of a distribution equilibrium it is reasonable to suggest that the relatively long action of bupivacaine might be due to its slower elimination from the body compared with shorter-acting local anesthetic agents. Values for the post-absorption distribution half-lives, 1/2, of a number of the latter are shown in table 1. These values, calculated from suitable data in the literature, are to a certain extent only approximate, but it is clear that lidocaine, prilocaine, mepivacaine and bupivacaine all have similar overall rates of elimination from the body. Consequently, the above hypothesis is not tenable.

An alternative supposition to explain the long duration of action may be found in the possibility of a slower removal of bupivacaine from the biophase and surrounding nerve tissue, which is irrespective of the rate of overall elimination from the body. Tucker et al. recently reported that bupivacaine is much more highly bound to plasma constituents than either lidocaine or mepivacaine, and furthermore, they found a good correlation between the extents of binding and the durations of anesthesia produced by these compounds.26 Although speculative, it is probable that binding to tissue proteins follows the same rank order as binding to plasma constituents and, therefore, it is not inconceivable to postulate that the higher binding affinity of bupivacaine is, in part, responsible for its longer duration of action compared with the other local anesthetics. This aspect is presently under investigation.

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References


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**Table 1. Overall Elimination Half-lives, 1/2, for Various Local Anesthetic Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>1/2 (hours)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidoacaine</td>
<td>600</td>
<td>2.6</td>
<td>21</td>
</tr>
<tr>
<td>With epinephrine</td>
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<td>4.0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>4.1</td>
<td>19</td>
</tr>
<tr>
<td>Prilocain</td>
<td>600</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>With epinephrine</td>
<td>600</td>
<td>2.1</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>2.3</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>2.5</td>
<td>18, 19</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>2.6</td>
<td>18</td>
</tr>
<tr>
<td>Mepivacain</td>
<td>450</td>
<td>2.6</td>
<td>19</td>
</tr>
<tr>
<td>With epinephrine</td>
<td>600</td>
<td>2.4</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>1.9</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>600</td>
<td>3.1</td>
<td>19</td>
</tr>
<tr>
<td>Bupivacain</td>
<td>150</td>
<td>2.4</td>
<td>This study</td>
</tr>
<tr>
<td>With epinephrine</td>
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<td>2.8</td>
<td>This study</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>3.6</td>
<td>This study</td>
</tr>
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</table>


Anesthesia

FETAL GLYCOGEN The fetal liver accumulates glycogen near the end of the gestation period for use immediately after parturition. From work presented it appears that at least three endocrine glands are involved in glycogen synthesis in the fetal liver: the fetal pituitary and adrenal cortex, which may control the synthesis of glycogen-forming enzymes, and insulin from the pancreas, possibly exercising control of the activity of existing enzyme proteins. These results are due to endogenous fetal insulin since the placental membranes are generally considered impermeable to insulin. (Manns, J. G., and Brockman, R. P.: The Role of Insulin in the Synthesis of Fetal Glycogen, Canad. J. Physiol. Pharmacol. 47: 917 (Nov.) 1969.)


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